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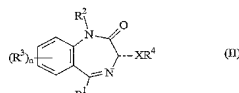
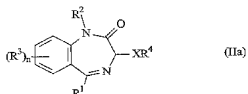
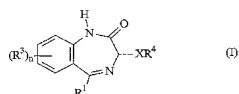
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(54) Title: PROCESS FOR PREPARING BENZODIAZEPINES



(57) Abstract: A process for producing a compound which is a benzodiazepine derivative of formula: (I) wherein: represents or R^1 represents C_{1-6} alkyl, aryl or heteroaryl; each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'/$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$, $-S(O)NR'/$ or $-S(O)_2NR'/$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl; n is from 0 to 3; X represents $-NH-$, $-N(C_{1-6}alkyl)-$, $-CO-$, $-CO-NR'-$, $-S(O)-$ or $-S(O)_2-$, wherein R' is hydrogen or a C_{1-6} alkyl group; and R^4 represents hydrogen; or $-CO-R^4$ or $-CO-NH-R^4$, wherein R^4 is a C_{1-6} alkyl, C_{1-6} hydroxyalkyl, aryl, heteroaryl, carbocyclyl or heterocyclyl group, which group is substituted by a C_{1-6} hydroxyalkyl, aryl, heteroaryl, carbocyclyl or heterocyclyl group or a $-(C_{1-4}alkyl)-X_1-(C_{1-4}alkyl)-X_2-(C_{1-4}alkyl)$ group, wherein X_1 represents $-O-$, $-S-$ or $-NR'-$, wherein R' represents

H or a C_{1-4} alkyl group and X_2 represents $-CO-$, $-SO-$ or $-SO_2-$; or R^4 represents $-A_1-Y-A_2$, wherein: A_1 is an aryl, heteroaryl, carbocyclyl or heterocyclyl group; Y represents a direct bond or a C_{1-4} alkylene, $-SO_2-$, $-CO-$, $-O-$, $-S$ or $-NR'-$, wherein R' is a C_{1-6} alkyl group; and A_2 is an aryl, heteroaryl, carbocyclyl or heterocyclyl group; or R^4 is a group selected from aryl- $C(O)-C(O)-$, heteroaryl- $C(O)-C(O)-$, carbocyclyl- $C(O)-C(O)-$, heterocyclyl- $C(O)-C(O)-$ and $-ZR^5$, wherein: Z represents $-CO-$, $-S(O)-$ or $-S(O)_2-$; and R^5 represents C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, aryl, heteroaryl, carbocyclyl, heterocyclyl, aryl- $(C_{1-6}alkyl)-$, heteroaryl- $(C_{1-6}alkyl)-$, carbocyclyl- $(C_{1-6}alkyl)-$, heterocyclyl- $(C_{1-6}alkyl)-$, aryl- $(C_{1-6}alkyl)-O-$, heteroaryl- $(C_{1-6}alkyl)-O-$, carbocyclyl- $(C_{1-6}alkyl)-O-$, heterocyclyl- $(C_{1-6}alkyl)-O-$ or $-NR'/$ wherein each R' and R'' is the same or different and represents hydrogen, C_{1-6} alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, aryl- $(C_{1-6}alkyl)-$, heteroaryl- $(C_{1-6}alkyl)-$, carbocyclyl- $(C_{1-6}alkyl)-$ or heterocyclyl- $(C_{1-6}alkyl)-$; or a pharmaceutically acceptable salt thereof; which process comprises: (a) subjecting a racemic benzodiazepine derivative of formula: (IIa): wherein R^1 , R^3 , R^4 , n and X are as defined above, and R^2 represents an amino protecting group, to crystallisation induced dynamic resolution to yield a benzodiazepine derivative of formula (II): wherein, R^1 , R^2 , R^3 , R^4 , n and X are as defined above; and (b) deprotecting the benzodiazepine derivative of formula (II) as defined above to yield a benzodiazepine derivative of formula (I) or a pharmaceutically acceptable form thereof as defined above.



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